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14. ABSTRACT

Prediction of blood transfusion needs and mortality for trauma patients in near real time is an unrealized goal. We hypothesized that analysis of pulse oximeter signals could predict blood transfusion and mortality as accurately as conventional vital signs(VSs).Continuous VS data were recorded for direct admission trauma patients with abnormal prehospital shock index (SI = heart rate [HR] / systolic blood pressure) greater than 0.62. Predictions of transfusion during the first 24 hours and in-hospital mortality using logistical regression models were compared with DeLong's method for areas under receiver operating characteristic curves (AUROCs) to determine the optimal combinations of prehospital SI and HR, continuous photoplethysmographic (PPG), oxygen saturation (SpO2), and HR-related features. We enrolled 556 patients; 37 received blood within 24 hours; 7 received more than 4 U of red blood cells in less than 4 hours or ''massive transfusion'' (MT); and 9 died. The first 15 minutes of VS signals, including prehospital HR plus continuous PPG, and SpO2 HR signal analysis best predicted transfusion at 1 hour to 3 hours, MT, and mortality (AUROC, 0.83; p G 0.03) and no differently (p = 0.32) from a model including blood pressure. Predictions of transfusion based on the first 15 minutes of data were no different using 30 minutes to 60 minutes of data collection. SI plus PPG and SpO2 signal analysis (AUROC, 0.82) predicted 1-hour to 3-hour transfusion, MT, and mortality no differently from pulse oximeter signals alone.
Pulse oximeter features collected in the first 15 minutes of our trauma patient resuscitation cohort, without user input, predicted early MT and mortality in the critical first hours of care better than the currently used VS such as combinations of HR and systolic blood pressure or prehospital SI alone.

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Automated prediction of early blood transfusion and mortality in trauma patients

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BACKGROUND: Prediction of blood transfusion needs and mortality for trauma patients in near real time is an unrealized goal. We hypothesized that analysis of pulse oximeter signals could predict blood transfusion and mortality as accurately as conventional vital signs (VSs).

METHODS: Continuous VS data were recorded for direct admission trauma patients with abnormal prehospital shock index (SI = heart rate [HR] / systolic blood pressure) greater than 0.62. Predictions of transfusion during the first 24 hours and in-hospital mortality using logistical regression models were compared with DeLong's method for areas under receiver operating characteristic curves (AUROCs) to determine the optimal combinations of prehospital SI and HR, continuous photoplethysmographic (PPG), oxygen saturation (SpO_2), and HR-related features.

RESULTS: We enrolled 556 patients; 37 received blood within 24 hours; 7 received more than 4 U of red blood cells in less than 4 hours or "massive transfusion" (MT); and 9 died. The first 15 minutes of VS signals, including prehospital HR plus continuous PPG, and SpO_2 HR signal analysis best predicted transfusion at 1 hour to 3 hours, MT, and mortality (AUROC, 0.83; $p < 0.03$) and no differently ($p = 0.32$) from a model including blood pressure. Predictions of transfusion based on the first 15 minutes of data were no different using 30 minutes to 60 minutes of data collection. SI plus PPG and SpO_2 signal analysis (AUROC, 0.82) predicted 1-hour to 3-hour transfusion, MT, and mortality no differently from pulse oximeter signals alone.

CONCLUSION: Pulse oximeter features collected in the first 15 minutes of our trauma patient resuscitation cohort, without user input, predicted early MT and mortality in the critical first hours of care better than the currently used VS such as combinations of HR and systolic blood pressure or prehospital SI alone. (*J Trauma Acute Care Surg*. 2014;76: 1379–1385. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic/prognostic study, level II.

KEY WORDS: Automated decision assist; photopletysmograph; blood transfusion; mortality.

Predicting the need for lifesaving interventions such as blood transfusion in near real time during resuscitation of trauma patients is an unrealized goal. Such predictions have the potential to provide prehospital decision assistance, triggering interventions for prehospital providers and combat medics, or could be integrated into future autonomous resuscitation systems to activate interventions by closed looped controllers to maintain physiologic stability until definitive care is initiated.[1] The pulse oximeter is a near-universally available source of continuous electronic data suitable for automated real-time prediction analysis.[2] The basic pulse oximeter was developed more than 70 years ago,[3,4] but only recently have inexpensive light emitting diodes and transistors allowed miniaturization as well as increased sensitivity, reliability, and reproducibility of the probe design. Pulse oximetry has been shown to identify critical postanesthesia events and reduce the need for emergency rescue teams by anticipating adverse events,[5] detecting airway obstruction,[6,7] diagnosing sleep apnea,[7,8] and predicting fluid responsiveness[9] and hypovolemia in anesthetized,[10,11] critically ill,[12] and hemorrhaging patients.[13] In comparison with these anesthesia/critical care recovery–related applications of pulse oximetry in relatively physiologically stable patients, we hypothesized that automated analysis of the photoplethysmograph (PPG) wave form and features of the pulse oximeter signal including heart rate (HR) per minute and percutaneous oxygen saturation (SpO_2%) during initial resuscitation of unstable trauma patients could predict the near-future use of blood transfusion, massive transfusion (MT), hospital length of stay (LOS) in days and in-hospital mortality

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as well or better than conventional indices based on manual collection of vital signs (VSs). Our objective was to test the potential of a noninvasive VS device as a platform for field-ready algorithms, which could be integrated into trauma patient monitoring systems.

PATIENTS AND METHODS

Enrollment Site and Criteria

Our Level 1 trauma center admits more than 5,000 trauma patients annually directly from the scene of injury, of whom 6% to 8% will require transfusion and 2% to 3% will require MT, defined in this analysis as more than 4 U of packed red blood cells in less than 4 hours. Most transfusions occur within the first few hours of admission and often occur as uncrossmatched universal donor group O blood on an emergency basis.[14–16] Adult (>17 years old) trauma patients who were admitted directly from the scene of injury were enrolled. Patients surviving less than 15 minutes were excluded. To dichotomize capture of representative populations highly likely or highly unlikely to be transfused or to die, we constructed a nomogram based on abnormal (>0.62) shock index (SI)[17] where SI is equal to HR per minute over systolic blood pressure (SBP in millimeters of mercury). Patients were eligible for enrollment if the SI, based on VS radioed in from the field by the emergency medical service (EMS) provider, was abnormal or they were rated EMS Priority 1 as critically ill or an injured person requiring immediate attention or unstable patients with life-threatening injury or illness without available prehospital VSs. To avoid potential confusion with neurogenic shock, cervical spine injury patients with neurologic deficit were excluded.

Data Collection

Continuous VS data, including VS wave forms, were collected via BedMaster software (Excel Medical Electronics, Jupiter, FL) in our 13-bay trauma resuscitation unit from the networked patient monitors (GE-Marquette-Solar-7000/8000, GE Healthcare, Little Chalfont, United Kingdom) using two VS data collection servers and one centralized VS data repository server. Electrocardiogram (ECG) and PPG wave forms were collected at 240 Hz. Numeric monitored trend values of HR (from both ECG and PPG), SpO_2, and intermittent values displaying noninvasive blood pressure (NIBP, mm Hg) were obtained every 5 seconds (0.2 Hz). The collected data were then compressed and transferred to the centralized VS data repository server through the hospital-secured intranet. VS data streaming rate after compression averaged 12 MB/h for wave forms and 76 KB/h for trend VS. One hour of continuous VS data were collected for analysis, beginning at the time of arrival in the trauma resuscitation unit. To ensure that monitoring artifact was not included in the data analysis, the collected data were filtered to reduce noise using a PPG signal quality index (PPG-SQI). The SQI was used to identify PPG signals when there was agreement between the pulse oximeter monitor pulse rate reading (PR1) and the automated PPG measurement of peak-to-peak distance (PR2). If $[(PR1 - PR2) / (PR1 + PR2) \times 0.5]$ showed greater than 5% difference, the wave form segment was excluded from the data set. Because more than 50% of PPG wave form (raw) data were available from the first 15 minutes, the first 30 minutes, and the first 60 minutes of patient monitoring after admission, these data were stratified for subanalysis.

Blood use was tracked by direct observation of resuscitation and by cross-validation with blood bank records tracking individual blood product unit types and time of release from the blood bank. Blood use predictions were partitioned into postadmission cohorts of MT and any transfusion within 24 hours. Blood use and patient demographics were entered into an Excel database (Microsoft, Redmond, WA). Transfusion was recorded for 37 patients (6.6%) in the first 24 hours and MT for 7 patients (0.01%).

Given our overall goal of early and automated prediction of transfusion need, MT, and mortality, we did not include laboratory results or imaging findings that have been used in published prediction algorithms for MT or trauma mortality[18] because these results are currently unavailable in the field before hospital admission. In-hospital mortality and hospital LOS were obtained from the trauma registry and predicted using Group 1 to 4 features (discussed later).

VS Features

HR, SBP, SI, and pulse oximeter data were compared using MatLab and MedCalc software (MatLab 7.13 R2011b, MathWorks, Natick, MA) to predict transfusion using features of these VS signals and combinations of these features. A custom PPG viewer was developed to display the first hour of PPG, ECG, HR, and SpO_2 features in 15-minute increments with user-configurable thresholds. Forty features of PPG, HR, and SpO_2 were defined. The 40 features included the following: 9 features included those describing the amplitude (in 10 percentiles) of the PPG signal and the remaining 3 PPG features included the 25th percentile and 75th percentile of the PPG amplitude and the PPG amplitude interquartile range (25th–75th percentile). Fourteen features were extracted from the percutaneous SpO_2 signal, including dose and percentage (SpO_2: ≤98%, ≤95%, ≤92%, ≤90%, and ≤86%) of abnormal SpO_2 during the data collection interval, and the mean value and quartiles of SpO_2 (25%, 50%, and 75%). Similarly, 14 features were extracted from the HR signal, including dose and percentage of abnormal HR (HR: ≥120, ≥110, ≥100, ≤72, and ≤60 beats/min), and the mean value and quartiles for HR (25%, 50%, and 75%). Areas under the receiver operating characteristic curves (AUROCs) were calculated for VS alone and a combination of VS and PPG features.

Data Analysis Groups

Data analysis focused on the comparison of transfusion predictions based on age- and sex-adjusted groups of VSs. Group 1 included only a single value of prehospital HR called in from the field; Group 2 included prehospital HR plus continuous analysis of PPG features; Group 3 included prehospital HR plus continuous analysis of PPG, HR, and SpO_2 features. Group 4 included prehospital SI plus PPG, HR, and SpO_2 features.

Statistical Analysis

For each data group, multiple logistic regression models, which were always adjusted for age and sex, were used for

TABLE 1. Age + Sex + Prehospital HR per Minute

Occurrence of Transfusion, Hours After Admission	Distribution Yes/No Transfusion			Group1: Age + Sex + Prehospital Heart Rate/min			
	Yes	No	Total	AUROC	95% CI	Sensitivity	Specificity
1–3 h	17	539	556	0.62	0.51–0.74	0.94	0.29
1–6 h	24	532	556	0.60	0.52–0.71	0.79	0.44
1–12 h	31	525	556	0.56	0.55–0.66	0.35	0.80
1–24 h	37	519	556	0.57	0.53–0.67	0.38	0.81

Numbers of patients transfused at each interval up to 24 hours after hospital admission. The AUROC, CI, sensitivity, and specificity are shown for Group 1 model of age- and sex-adjusted transfusion predictions using prehospital HR per minute.

prediction of transfusion, MT, LOS, and mortality. The best combination of VS features included in each prediction model was selected based on a stepwise procedure. AUROCs under prediction models were compared using DeLong's method.[19] Sensitivity and specificity were calculated from the optimal threshold determined by Youden index. The prediction models were cross-validated by training and testing using leave-one-out methodology.[20]

RESULTS

After institutional review board approvals by expedited review were obtained, with a waiver of regulatory requirement for obtaining or documenting informed consent from both the University of Maryland and US Air Force Institutional Review Board, the initial 1 hour of continuous VS data, including PPG and ECG wave forms and VS trends, were collected on the 556 patients who met enrollment criteria between December 2011 and June 2012. Fifty-two patients were enrolled because of Priority 1 criteria, and mortality was 5.8% transfusion within 24 hours was 17.3%, and MT occurred in two Priority 1 patients (3.8%). In SI criteria, enrolled patients' (90.7% of the total enrollments) mortality was 1.2%, transfusion within 24 hours was 6.4%, and MT occurred in five patients (1%). Demographics of enrolled patients included a mean (SD) age of 40.3 (16.7) years, with a mean Glasgow Coma Scale (GCS) score of 14.2. Males constituted 68.5% (381 of 556) of the study group; 470 (84.5%) experienced blunt trauma, and 56 (10.1%) experienced penetrating injury. Mechanisms of injury included motor vehicle–related incidents (261, 46.9%), falls (145, 26%), and interpersonal violence (89, 16.5%). Most patients (547, 98.4%) were discharged home or to institutional care; 9 died in the hospital (1.6%). Overall trauma center patient in-hospital mortality during the enrollment interval was 3.8%, and overall mortality caused by blunt and penetrating injuries was both also 3.8%, so the study cohort sustained lower degrees of injury compared with the overall population. In the study cohort, we excluded patients dying within the first 15 minutes after trauma center arrival. In addition, we were unable to collect PPG wave forms during patient movement to the computed tomographic (CT) scan or operating room, which occurred early in the care of sick patients with higher likelihood of dying.

Analyses Using VS and PPG Wave Form Data Without SI

Comparisons of AUROC in Groups 1 to 4 were made using the noise-reduced signals to select the best analytic model for the collected data. Noise reduction by PPG-SQI removed artifacts in the pulse oximeter data associated with patient resuscitation, including 29.3% of the data recorded in the first 15 minutes, 25.5% of the data recorded in the first 30 minutes, and 29.3% of the data recorded in the first 60 minutes (Tables 1–3). Results for the prediction of transfusion within the selected intervals, confidence intervals (CIs), sensitivity, and specificity of prediction are shown in Tables 1 to 3. Group 1 (prehospital HR only) AUROC for all postadmission time intervals ranged from 0.56 to 0.62 (Table 1). When compared with Group 1, the addition of PPG features alone (Group 2, Table 2) improved AUROCs to 0.74 to 0.89, and the addition of PPG with SpO_2 and HR features (Group 3, Table 3), improved AUROCs to 0.79 to 0.9 in all postadmission times and data collection intervals in comparison with the Group 1 model and in comparison with 1-hour to 3-hour and 1-hour to 12-hour transfusion predictions in the Group 2 model. Increasing duration of data collection beyond 15 minutes

TABLE 2. Age + Sex + Prehospital Heart Rate per Minute + PPG Waveform Features

Occurrence of Transfusion, Hours After Admission	15-min PPG Duration				30-min PPG Duration				60-min PPG Duration			
	AUROC	95% CI	Sensitivity	Specificity	AUROC	95% CI	Sensitivity	Specificity	AUROC	95% CI	Sensitivity	Specificity
1–3 h	0.78	0.65–0.92	0.76	0.78	0.89	0.81–0.97	0.94	0.70	0.80	0.69–0.91	0.71	0.81
1–6 h	0.84	0.76–0.93	0.79	0.80	0.83	0.74–0.92	0.88	0.72	0.78	0.68–0.87	0.67	0.78
1–12 h	0.81	0.71–0.90	0.71	0.87	0.80	0.70–0.90	0.65	0.89	0.76	0.66–0.86	0.58	0.90
1–24 h	0.74	0.65–0.84	0.68	0.75	0.78	0.69–0.87	0.78	0.72	0.79	0.70–0.87	0.68	0.82

AUROC, CI, sensitivity, and specificity for Group 2 model of age- and sex-adjusted transfusion predictions using prehospital heart rate per minute plus PPG waveform features with three durations of data collection of 15, 30, and 60 minutes.

TABLE 3. Age + Sex + Prehospital HR + PPG Waveform Features + SpO_2 and HR Features

Occurrence of Transfusion, Hours After Admission	15-min PPG Duration + SpO_2+ HR				30-min PPG Duration + SpO_2 + HR				60-min PPG Duration + SpO_2 + HR			
	AUROC	95% CI	Sensitivity	Specificity	AUROC	95% CI	Sensitivity	Specificity	AUROC	95% CI	Sensitivity	Specificity
1–3 h	0.83	0.72–0.95	0.76	0.83	0.90	0.82–0.98	0.94	0.79	0.89	0.82–0.96	0.76	0.90
1–6 h	0.86	0.78–0.94	0.92	0.72	0.85	0.76–0.94	0.83	0.77	0.81	0.71–0.91	0.79	0.72
1–12 h	0.86	0.79–0.93	0.77	0.85	0.80	0.72–0.89	0.74	0.78	0.79	0.69–0.88	0.87	0.59
1–24 h	0.81	0.72–0.90	0.78	0.80	0.82	0.74–0.90	0.86	0.71	0.82	0.74–0.89	0.78	0.73

AUROC, CI, sensitivity, and specificity for Group 3 model of age- and sex-adjusted transfusion predictions using prehospital heart rate per minute plus PPG waveform plus percutaneous oxygen saturation (SpO_2%), and continuous pulse oximetry heart rate(HR/min) features with three durations of data collection of 15, 30, and 60 minutes.

did not improve 1-hour to 3-hour transfusion predictions for Group 3. Intergroup comparisons show that Groups 2 and 3 predicted transfusion in the first 3 hours of care better than Group 1 ($p < 0.034$ for Group 2, $p < 0.003$ for Group 3).

Comparisons of Prediction of Transfusion Using Pulse Oximetry–Derived Features Alone Versus Pulse Oximetry Plus NIBP–Derived Features; Cross-Validation of Prediction Models

In comparison with pulse oximeter–derived features alone (Groups 2–3) and pulse oximeter plus NIBP–derived features (Group 4), the addition of SI did not significantly improve transfusion prediction outcomes at any interval of blood use within 24 hours after admission ($p = 0.1–1.0$) (Table 4). Cross-validation of the prediction models by leave-one-out methodology based on prehospital HR, PPG, SpO_2, and pulse oximetry–derived features (Group 3) and prehospital SI and PPG, SpO_2, and pulse oximetry–derived features (Group 4) show the robustness of these models, giving an overall AUROC of 0.83 to predict blood transfusion within 1 hour to 3 hours for the Group 3 model versus AUROC of 0.80 for the Group 4 model, which included SI (Table 5).

Prediction of MT of Greater Than 4 Units in Less Than 4 Hours (MT)

Group 3 data predictions of MT (AUROC, 0.94) were significantly ($p < 0.02$) better than those of Group 1 (AUROC, 0.75) and Group 2 data (AUROC, 0.87; $p < 0.04$) and no different ($p = 0.32$) from Group 4 data (AUROC, 0.88). Results of training and testing for Group 3 and 4 data are shown in Table 6.

Prediction of Mortality and Hospital LOS in Days

Group 3 data, pulse oximeter features alone, gave an overall AUROC of 0.94 for mortality and 0.72 for LOS. This was significantly better ($p < 0.003–0.001$) than with Group 1 and 2 data and no different from Group 4 data (AUROC, 0.94 for mortality; AUROC, 0.71 for LOS; $p = 0.32$) (Table 6).

DISCUSSION

Automated continuous analysis of PPG features, including HR, SpO_2, and wave form analysis collected for 15 minutes and without additional user input, predicted the use of both any transfusion and MT in early resuscitation no differently from the current best predictors that use prehospital SI (including SBP) or HR alone. At present, SI is used as baseline VS in emergency transfusion decision making.[21–23] SI based on field VS has been shown to be correlated with transfusion, where SI of 0.9 to1.1 had a 1.5-fold increased risk (RR, 1.61; 95% CI, 1.13–2.31) for transfusion of greater than 10 U of red blood cells in 24 hours, the traditional definition of MT.[21]

SI of 1 or greater has also been suggested as a field transfusion decision tool[23] and as a measure of hospital resource use and mortality.[24] SI at trauma center admission decreases (lower HR, higher SBP) with age,[25] and SI differences by sex are present across all age groups (including children).[26] However, in our model, age- and sex-adjusted SI did not contribute to either increased sensitivity (who would receive blood at all) or specificity (who would receive blood within a narrow early time frame—the first 6 hours—critical to the rescue of a massively hemorrhaging patient). Predictions of blood use 1 hour to 24 hours beyond the initial 1-hour data collection have the lowest AUROC of predictions across all

TABLE 4. Age + Sex +Pre-SI + PPG Waveform Features + SpO_2 and HR Features

Occurrence of Transfusion, Hours After Admission	15-min PPG Duration + SpO_2 + HR				30-min PPG Duration + SpO_2 + HR				60-min PPG Duration + SpO_2 + HR			
	AUROC	95% CI	Sensitivity	Specificity	AUROC	95% CI	Sensitivity	Specificity	AUROC	95% CI	Sensitivity	Specificity
1–3 h	0.80	0.68–0.93	0.76	0.80	0.88	0.80–0.97	0.94	0.73	0.84	0.75–0.94	0.82	0.74
1–6 h	0.85	0.77–0.94	0.79	0.84	0.87	0.80–0.94	0.88	0.75	0.80	0.70–0.90	0.79	0.71
1–12 h	0.81	0.72–0.91	0.81	0.82	0.83	0.75–0.92	0.87	0.70	0.79	0.69–0.89	0.65	0.86
1–24 h	0.81	0.73–0.89	0.81	0.78	0.80	0.71–0.89	0.68	0.82	0.80	0.71–0.88	0.86	0.64

AUROC, CI, sensitivity, and specificity for Group 4 model of age- and sex-adjusted transfusion predictions using prehospital SI plus PPG waveform plus percutaneous oxygen saturation (SpO_2%), and continuous pulse oximetry heart rate features (HR/min) with three durations of data collection of 15, 30, and 60 minutes.

TABLE 5.

Occurrence of Transfusion, Hours After Admission	Group 3			Group 4		
	15-min Prehospital HR + PPG Duration + SpO_2/HR Features			15-min Prehospital SI + PPG Duration + SpO_2/HR Features		
	Train AUROC	Test AUROC	Overall AUROC	Train AUROC	Test AUROC	Overall AUROC
1–3 h	0.85	0.74	0.83	0.81	0.75	0.80
1–6 h	0.87	0.73	0.86	0.86	0.80	0.85
1–12 h	0.87	0.77	0.86	0.82	0.74	0.81
1–24 h	0.82	0.75	0.81	0.82	0.75	0.81

Group 3 and 4 model performance during training and testing using leave-one-out methodology and the overall AUROC of the two best models in predicting transfusion at intervals within 24 hours of hospital admission using 15 minutes of data collection.

groups, probably owing to confounding variable of interventions occurring after early resuscitation. Experience using SI suggests that SI can be a sensitive index of hypovolemia,[17] but the traditional definition of MT of 10 or more units in 24 hours is not adequately specific to elucidate actual blood use or need in massively bleeding patients.[15]

Six scoring systems including Trauma-Associated Severe Hemorrhage (TASH) score, Prince of Wales Hospital Hong Kong Score, Assessment of Blood Consumption Score, and those described using military penetrating trauma populations[27,28] predict ongoing hemorrhage and transfusion after severe trauma with AUROC of 0.889 (TASH) to 0.763 (Assessment of Blood Consumption Score) in blunt trauma and AUROC of 0.823[27] to 0.8[28] in penetrating trauma.[18] The strengths and limitations of the six MT scoring systems, together with additional MT predictors, have recently been reviewed.[29] Advanced radiologic tools such as CT scan and Focused Assessment with Sonography in Trauma (FAST) scans and laboratory analyses (hemoglobin, base excess, international normalized ratio, lactate) that are not routinely available in most prehospital en route care or austere military environments are needed to make these predictions, hours after they would be useful clinically or of assistance to the blood bank in implementation of MT protocols. Our predictions, which had an AUROC of 0.83 for prediction of any blood use within 3 hours and of 0.92 for MT using Group 3 data, used continuous data captured from a single VS instrument (pulse oximeter) and required no user input or blood samples or scans. Group 4 data, which required the addition of SBP data from a NIBP monitor, gave an overall AUROC of 0.80 when validated for prediction of blood use within 3 hours and of 0.88 for MT. Inclusion of SI would require both interfaces with simultaneous use and colocation of an NIBP device. A monitoring and decision assist system built on these data would only provide updated information at NIBP cycling intervals (usually once per 5 minutes). In contrast, pulse oximetry data are continuously updated.

Inclusion of respiratory rate may improve predictions of blood use. Previous efforts have examined respiratory-induced variation of the PPG wave form associated with hypovolemia in spontaneously breathing trauma patients used 45-second to 60-second intervals of "clean" prehospital resuscitation data. Chen et al.[13] found that peak height and amplitude interquartile ranges were different ($p < 0.01$) in control versus hemorrhaging patients (AUROC, 0.65; 95% CI, 0.5–0.7). These authors used ECG, PPG, respiratory rate, HR, SBP, diastolic blood pressure, and SpO_2 recorded from conventional EMS equipment via three separate VS signals and found that their PPG metrics weakly correlated with transfusion requirements. In 26 of 344 patients who were transfused, correlation ($r = 0.39$) between peak height of PPG and transfusion was not significant. One reason that we may have found improved prediction of transfusion is that we analyzed a longer interval of PPG signals and more features of these signals and had a greater absolute number of patients who received transfusion. We did analyze transfusion predictions using data collection periods shorter than 15 minutes; however, of the initial 5 minutes of data, less than 50% of the signals were useable after application of SQI. Analysis of these data gave an AUROC of 0.70 for prediction of blood transfusion within 6 hours, significantly different ($p < 0.005$) from predictions based on 15 minutes of data (AUROC, 0.86). The application of SQI allowed for the use of approximately 30% of the resuscitation data, owing to artifacts produced by motion and patient care interventions.

We have also considered the possible addition of continuous noninvasive hemoglobin measurement[30] and PPG-derived respiratory rate[31,32] to our model. Currently, continuous noninvasive hemoglobin measurement requires specialized proprietary software and sensors, which would not be available as

TABLE 6.

15-min PPG Duration Prediction	Group3: HR + PPG, SpO_2/HR Features			Group4: SI + PPG, SpO_2/HR Features		
	Train AUROC	Test AUROC	Overall AUROC	Train AUROC	Test AUROC	Overall AUROC
Mortality	0.94	0.88	0.94	0.94	0.86	0.94
LOS > 3 d	0.73	0.69	0.72	0.71	0.68	0.71
Transfusion > 4 U in <4 h	0.94	0.65	0.92	0.89	0.66	0.88

Group 3 and 4 model performance during training and testing using leave-one-out methodology, and the overall AUROC of the two best models in predicting transfusion of greater than 4 U of blood in less than 4 hours, hospital LOS greater than 3 days, and in-hospital mortality using 15 minutes of data collection.

a legacy retrofit into existing EMS prehospital devices. Nevertheless, such capacity may be available in future generations of monitors, and use of those data should be tested in future prediction models, although such data are reported to have limitations in usefulness during trauma patient resuscitation.[33] Respiratory rate derived from PPG wave forms seems to have some efficacy in stable patients but, like ECG-derived respiratory rate, has significant artifact in real-world situations owing to sensor movement and dislodgment.[31]

There are several limitations worth noting. Data were obtained after arrival at the trauma center and do not reflect immediate postinjury physiology. In addition, data were not collected on every eligible patient admitted during the data collection period for a variety of logistical reasons including multiple simultaneous patient admissions, concerns with interruption of emergency clinical care (especially in those mortally injured), emergency patient admissions occurring without sufficient notice to set up the data collection process, movements of seriously injured patients rapidly to a CT scan or the operating room soon after admission, so that enrolled patients had more modest injury, lower mortality, and greater representation of blunt trauma mechanism compared with the entire cohort of eligible admissions because of these logistical reasons. However, it should be noted that the study cohort showed a blood transfusion rate (6.6%), MT rate (up to 3.8%), and LOS similar to our overall population..

Loss of data from 47 patients occurred during a relocation of the data collecting servers for renovation of the network hub. However, data regarding demographics, injury mechanisms, and severity of injury match those of the total population admitted during this same period and are likely to represent a valid study population. Our patient sample size was relatively small and included only 10% of penetrating trauma mechanism of injury[34] although the transfusion rate (6.6%) of patients in our enrolled cohort was typical. The power of our analytic algorithm for predicting transfusion may have different results in penetrating trauma and military injuries and mortally injured populations.

Despite the these limitations, the work we present here shows that targeted pulse oximeter features collected in the first 15 minutes of trauma resuscitation can accurately predict transfusion, MT, LOS, and mortality in the critical first hours of care. Given the 27-minute mean en route transit time for our helicopter EMS[35] and similar, if not longer, transport times in wartime environments, prehospital collection of data sufficient to warn the trauma receiving team and, through them, the blood bank, of impending need for increased blood product support is now potentially feasible. This work also supports the preliminary efforts of trauma care and EMS systems to forward-deploy instrumentation capable of automated collection of continuous, high-quality VS data as our data analysis process used all the available data without selection of data segments. The method described was specifically targeted for processing real-time high-resolution wave forms. Innovative use of these data will then support ongoing development of the analytic platforms for future generations of clinical decision support instrumentation.

In conclusion, automated prediction of immediate and MT and mortality for trauma patients is described. We enrolled 556 trauma patients in this study, 37 of whom received transfusions, 7 received more than 4 U in the first 4 hours (MT), and 9 died. Pulse oximeter features collected in the first 15 minutes of our trauma patient resuscitation cohort predicted transfusion, MT, LOS, and mortality without user input, in the critical first hours of care and performed better than the currently used VS such as combinations of HR or prehospital SI alone.

AUTHORSHIP

C.F.M. obtained funding and contributed in the literature search, study design, data analysis, interpretation, and writing. Y.W. performed the data analysis. P.F.H. contributed in the study design as well as data collection, analysis, and interpretation. S,-Y.C. performed the data analysis. H.H.C. contributed in the study design and statistical analyses. G.H. performed the data collection. L.G.S. contributed in the study design, data analysis, interpretation, and writing. S.S. performed the data interpretation and writing.

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REFERENCES

1. Palmer RW. Integrated diagnostic and treatment devices for en route critical care of patients within theater. Proceedings of NATO RTO symposium on use of advanced technologies and new procedures in medical field operations. RTO-MP-HFM-182 April 2010:37-1-12.
2. Shelley KH. Photoplethysmography: beyond the calculation of arterial oxygen saturation and heart rate. *Anesth Analg*. 2007;105:S31–S35.
3. Molitor H, Kniazuk M. A new bloodless method for continuous recording of peripheral circulatory changes. *J Pharmacol Exp Ther*. 1936; 57:6–18.
4. Hertzman AB. The blood supply of various skin areas as estimated by the photoelectric plethysmograph. *Am J Physiol*. 1938;214:328–340.
5. Taenzer HA, Pyke JB, McGrath SP, Blike GT. Impact of pulse oximetry surveillance on rescue events and intensive care unit transfers: a before and after concurrence study. *Anesthesiology*. 2010;112:282–287.
6. Gil E, Bailon R, Vergara JM, Laguna P. PTT variability for discrimination of sleep apnea related decreases in amplitude fluctuations of PPG signal in children. *IEEE Trans Biomed Eng*. 2010;57:1079–1088.
7. Knorr-Chung BR, McGrath SP, Blike GT. Identifying airway obstruction using photoplethysmography (PPG). *J Clin Monit Comput*. 2008; 22:95–101.
8. Gil E, Mendez M, Vergara JM, Cerutti S, Bianchi AM, Laguna P. Discrimination of sleep-apnea-related decreases in the amplitude fluctuations of PPG signal in children by HRV analysis. *IEEE Trans Biomed Eng*. 2009;56:1005–1014.
9. Loupec T, Nanadoumgar H, Frasca D, Petitpas F, Laksiri L, Baudouin D, Debaene D, Dahyot-Fizelier C, Mimoz O. Pleth variability index predicts fluid responsiveness in critically ill patients. *Crit Care Med*. 2011; 39:294–299.
10. Cannensson M, Desebbe O, Rosamel P, Delannoy B, Robin J, Bastien O, Lehot J. Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. *Br J Anaesth*. 2008;101:200–206.

11. Forget P, Lois F, de Kock M. Goal directed fluid management based on pulse-oximeter derived pleth variability index reduces lactate levels and improves fluid management. *Anesth Analg*. 2010;111:910–914.
12. Partridge BL. Use of pulse oximetry as a non-invasive predictor of intravascular volume status. *J Clin Monit*. 1987;3:236–238.
13. Chen L, Reisner AT, Gribok A, Reifman J. Is respiration-induced variation in the photoplethysmogram associated with major hypovolemia in patients with acute traumatic injuries? *Shock* 2010;34:455–460.
14. Como JJ, Dutton RP, Scalea TM, Edeleman BB, Hess JR. Blood transfusion rates in the care of acute trauma. *Transfusion*. 2004;44:809–813.
15. de Biasi AR, Stansbury LG, Dutton RP, Stein DM, Scalea TM, Hess JR. Blood product use in trauma resuscitation: plasma deficit versus plasma ratio as predictors of mortality in trauma. *Transfusion*. 2011;51:1925–1932.
16. Murthi SB, Stansbury LG, Dutton RP, Edelman BB, Scalea TM, Hess JR. Transfusion medicine in trauma patients: an update. *Expert Rev Hematol*. 2011;4(5):527–537.
17. Birkhahn R, Gaeta T, Terry D, Bove J, Tloczkowski J. Shock index in diagnosing early acute hypovolemia. *Am J Emerg Med*. 2005;23:323–326.
18. Brockamp T, Nienaber U, Mutschler M, Wafaisade A, Peiniger S, Lefering R, Bouillon B, Maegele M. Predicting on-going hemorrhage and transfusion requirement after severe trauma: a validation of six scoring systems and algorithms on the TraumaRegister DGU®. *Crit Care*. 2012; 16(4):R129.
19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
20. Bishop CM. *Pattern Recognition and Machine Learning*. New York, NY: Springer; 2006:1–66.
21. Vandromme MJ, Griffin RL, Kerby JD, McGwin G, Rue LW, Weinberg JA. Identifying risk for massive transfusion in the relatively normotensive patient: utility of the prehospital shock index. *J Trauma*. 2011;70:384–390.
22. Guidelines for field triage of injured patients; Recommendations of the National Expert Panel on Field Triage. *MMWR Recomm Rep*. 2009; 58(RR-1)1–35. www.cdc.gov/mmwr.
23. Mitra B, Fitzgerald M, Chan J. The utility of a shock index ≥ 1 as an indication for pre-hospital oxygen carrier administration in major trauma. Injury 2013. Available at: http://www.sciencedirect.com/science/article/pii/S0020138313000223. Accessed February 4, 2013.
24. McNab A, Burns B, Bhullar I, Chesire D Kerwin A. A prehospital shock index for trauma correlates with measures of hospital resource use and mortality. *Surgery.* 2012;152:473–476.
25. Zarzaur BL, Croce MA, Fischer PE, Magnotti LJ, Fabian TC. New vitals after injury: shock index for the young and age x shock index for the old. *J Surg Res*. 2008;147:229–236.
26. Rapapaport LD, Deakyne S, Carcillo JA, Mc Fann K, Sills MR. Age- and sex-specific normal values for shock index in National Health and Nutrition Examination survey 1999–2008 for ages 8 years and older. *Am J Emerg Med*. 2013;31:838–842.
27. Larson CR, White CE, Spinella PC, Jones JA, Holcomb JB, Blackbourne LH, Wade CE. Association of shock coagulopathy, and initial vital signs with massive transfusion in combat casualties. *J Trauma*. 2010;69(Suppl 1):S26–S32.
28. Screiber M, Perkins J, Kiraly L, Underwood S, Wade C, Holcomb JB. Early predictors of massive transfusion in combat casualties. *J Am Coll Surg*. 2007;205:541–545.
29. Shackelford S, Colton K, Stansbury LG, Galvagno SM, Anazodo AN, DuBose JJ, Hess J R, Mackenzie CF. Early identification of uncontrolled hemorrhage after trauma: current status and future direction. *J Trauma Acute Care Surg*. 2014.
30. Barker SJ, Badall JJ. The measurement of dyshemoglobins and total hemoglobin by pulse oximetry. *Curr Opin Anaesthesiol*. 2008;21:805–810.
31. Nitzan M, Babchenko A, Khanokh B, Landau D. The variability of the photoplethysmograph signal: a potential method for evaluation of the autonomic nervous system. *Physiol Meas*. 1998;19:93–102.
32. Addison PS, Watson JN, Mestek ML, Mecca RS. Developing an algorithm for pulse oximetry derived respiratory rate (RR(oxi)): a healthy volunteer study. *J Clin Monit Comput*. 2012;26(1):45–51.
33. Mackenzie CF, Anazodo A, Hu PF, Hagengeorge G, Imle C, Stansbury L, Miller C, Chen H, Dinardo T, Hardinger H, et al.; ONPOINT Investigator Group. Can non-invasive hemoglobin predict universal donor blood or urgent transfusion use during trauma patient resuscitation? *Crit Care Med*. 2012;40(12):Abstract 755.
34. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997–2008. *J Trauma*. 2010;69(3): 620–626.
35. MIEMSS 2013 Report pp 1–90 http://www.miemss.org/home/LinkClick.aspx?fileticket=J_mUzrbEn4I%3D&tabid=58&mid=448.

